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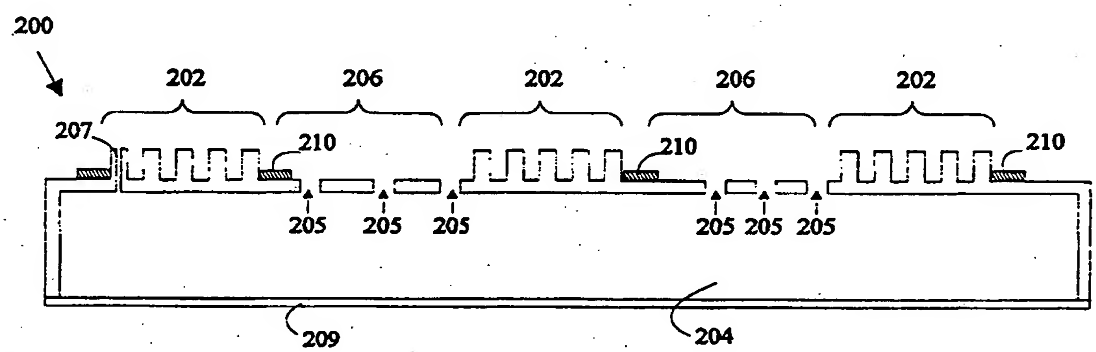

(57) Abstract

A drug delivery system. The system includes an apparatus (200) for mechanically disrupting a layer of skin having a known thickness without substantially disrupting underlying dermis layers below the layer of skin in question and a reservoir (204) for continuously applying the drug to the disrupted area of skin. The apparatus (200) includes a cutter having a plurality of microprotrusions (202) having a height less than or equal to the thickness of the layer of skin and a stop for preventing the apparatus (200) from penetrating said layer of skin beyond a predetermined distance. In the preferred embodiment of the present invention, the microprotrusions (202) comprise first and second groups of microprotrusions (202) extending from a substrate which is communicating with the drug reservoir (204), and the stop comprises a region of the substrate separating the first and second groups and recessed below the tops of the first and second groups of microprotrusions (202). Channels through the stop region into the drug reservoir (204) allow the drug to medicate the disrupted area in one embodiment of the present invention. In a second embodiment of the present invention, the channels are provided in the microprotrusions (202).

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MICROMECHANICAL PATCH FOR ENHANCING THE DELIVERY OF COMPOUNDS THROUGH THE SKIN

Field of the Invention

The present invention relates to drug delivery systems, and more particularly, to a mechanical device that alters the outermost layer of skin for the improved delivery of compounds through the skin.

Background of the Invention

Transdermal delivery of medication is well known in the prior art. Transdermal patches are available for a number of drugs. Commercially available examples of transdermal patches include scopolamine for the prevention of motion sickness, nicotine for aid in smoking cessation, nitroglycerin for the treatment of coronary angina pain, and estrogen for hormonal replacement. Generally, these systems have drug reservoirs sandwiched between an impervious backing and a membrane face which controls the steady state rate of drug delivery. The systems usually are attached to the skin by an adhesive gel with the membrane face adjacent to the skin..

Transdermal medication has significant advantages over both hypodermic injection and oral administration. A transdermal patch can provide significantly greater effective blood levels of a beneficial drug because the drug is not delivered in spike concentrations as is the case with hypodermic injection and most oral administration. In addition, drugs administered via transdermal patches are not subjected to the harsh environment of the digestive tract. Hence, in principle, transdermal delivery provides a method for administrating drugs that would otherwise need to be administered via hypodermic injection or intravenous infusion because the drug is destroyed in the digestive tract or immediately absorbed by the liver. Conversely, the digestive tract and liver are not subjected to the drug in transdermal administration. Many drugs, such as aspirin, have an adverse effect on the digestive tract.

Prior art transdermal drug delivery systems may be divided into passive diffusion and active transport systems. Transdermal drug delivery by diffusion is by far the most common

of the transdermal methods. The nicotine patch is an example of this method of delivery (U.S. Patent #4,597,961 to Frank T. Etscorn). This process is based on presenting the medication in a high dose external to the dermis and allowing the chemical to diffuse into and through the skin. The degree of diffusion depends on the porosity of the skin, the size and polarity of the drug molecules, and the concentration gradient across the stratum corneum, the outermost layer of human skin. These factors generally limit this mode of delivery to a very small number of useful drugs with very small molecules or unique electrical characteristics.

Attempts to widen the range of drugs that may be transdermally delivered have led to the active methods mentioned above. The active diffusion systems involve iontophoresis, electroporation and ultrasound to increase the migration of the drug across the skin barrier. These methods attempt to electrically assist diffusion of the medication or apply high frequency electrical pulses or sound waves to the skin to improve absorption. Unfortunately, the high cost and inconvenience of providing portable electrical equipment have limited the commercial application of such active systems.

Accordingly, it is a general object of the present invention to provide an improved transdermal drug delivery system and method.

It is another object of the invention to eliminate or greatly reduce the pain of drug delivery by present skin-penetrating devices, such as needles, fluid jets, iontophoresis, etc.

It is another object of the present invention to provide a transdermal delivery system that does not rely on applied electric fields, yet allows drugs that could not previously be administered by passive diffusion to be so administered.

These and other objects of the present invention will become apparent to those skilled in the art from the following detailed description of the invention and the accompanying drawings.

Summary of the Invention

The present invention comprises a drug delivery system including an apparatus for mechanically disrupting a layer of skin having a known thickness without substantially disrupting underlying dermis layers below the layer of skin in question and a reservoir for continuously applying the drug to the disrupted area of skin. The apparatus includes a cutter having a plurality of microprotrusions having a height less than or equal to the thickness of the layer of skin and a stop for preventing the apparatus from penetrating said layer of skin beyond a predetermined distance. In the preferred embodiment of the present invention, the microprotrusions comprise first and second groups of microprotrusions extending from a substrate which is communication with the drug reservoir, and the stop comprises a region of the substrate separating the first and second groups and recessed below the tops of the first and second groups of microprotrusions. Channels through the stop region into the drug reservoir allow the drug to medicate the disrupted area in one embodiment of the present invention. In a second embodiment of the present invention, the channels are provided in the microprotrusions.

Brief Description of the Drawings

Figure 1 is a cross-sectional view of a micromechanical patch according to the present invention.

Figures 2-5 are cross-sectional views of a silicon substrate at various stages in the fabrication of a bed of microprotrusions according to the present invention.

Figure 6 is a cross-sectional view of a mold and a bed of microprotrusions constructed thereon.

Detailed Description of the Invention

The major limitation of current transcutaneous drug delivery systems is the inability or difficulty in diffusing the delivered drug through the stratum corneum, the outer approximate 10 μm of the skin over most of the body. The stratum corneum is a thin layer of dead skin cells that covers the epidermis and dermis layers of skin. Although only about 10 cells thick, the stratum corneum layer keeps water in the human body from evaporating through the skin. This critical role as a diffusion barrier for the prevention of water evaporation also serves to make the skin impermeable to the diffusion of most beneficial drugs from outside the body.

The present invention is based on mechanically penetrating or disrupting the stratum corneum layer, thereby improving the effectiveness of transdermal delivery of drugs incapable of diffusion through the stratum corneum. The simplest embodiment of the present invention comprises a bed of microneedles or microcutters that are just long enough to effectively penetrate the stratum corneum. This bed of microprotrusions can be placed on the skin and moved relative to it, either vertically and/or horizontally, in order to generate a large number of tiny micropenetrations and/or microdisruptions in the stratum corneum layer. This bed of microprotrusions can be inexpensively manufactured by one of several technologies commonly referred to as micro-machining (micro-mechanics, Micro Electro Mechanical Systems, known as MEMS, etc.).

The problems introduced by the stratum corneum have been recognized for some time. However, previous techniques for removal of the stratum corneum have introduced new problems which have prevented their commercial use. For example, techniques in which the stratum corneum is removed by placing sticky tape in contact with the skin and then ripping off the tape have been used. Unfortunately, such techniques are painful and, in addition, remove significant amount of underlying epidermis and dermis layers. The loss of the additional layers of skin can result in bleeding and the possibility of infection. Such techniques are impractical for clinical practice, and disrupt the skin such that healing takes a week or longer.

The present invention, however, utilizes a mechanical method for penetrating the stratum corneum layer without substantially damaging the underlying layers. Hence, blood vessels and nerve endings are not damaged. The simplest embodiment of the present invention is a bed of microprotrusions 202 attached to a drug reservoir 204 as shown in Figure 1 which is a cross-sectional view of a drug delivery patch 200 according to the present invention. Drug reservoir 204 includes a number of channels 205 through which a drug stored in reservoir 204 can move from reservoir 204 to the skin area adjacent to the disruptions. The areas 206 between the groups of microprotrusions also act as a penetration "stop" that prevents the microprotrusions from penetrating the skin to a depth substantially greater than the height of the microprotrusions. While the drug passages 205 are shown in the stop regions, it will be apparent to those skilled in the art that the passage could be placed in the microprotrusions as shown at 207 to convert the protrusion to a "microneedle".

The manner in which such a bed of microprotrusions can be constructed is illustrated in Figures 2-6. Refer first to Figures 2-5 which illustrate one of several methods for the fabrication of a bed of microprotrusions in a silicon substrate 13. A layer 12 of silicon dioxide is first deposited on substrate 13. A layer 11 of photoresist is then deposited on oxide 12 and patterned using conventional photolithography techniques. The patterned photoresist layer is used to control the etching of the oxide layer using a fluorine reactive ion etch process which stops on the silicon. The patterned oxide layer is then used as a mask for a chlorine reactive ion etch that penetrates the silicon substrate leaving protrusions 16. The intermediate oxide masks ensure straight sidewalls and consistent edge depths. Alternatively, the microcutter may be composed of the structure shown in Figure 3 after the top layer of photoresist 11 is removed, provided the silicon oxide layer 12 is deposited with a thickness approximately to the stratum corneum thickness.

Yet another alternative method for generating a bed of microprutrusions comprising a bed of microprotrusions is illustrated in Figure 6 which is a cross-sectional view of a mold 24 used to fabricate, for example, a plastic/polymer microcutter 22. Plastic/polymer structures having features of the same general dimensions as those needed for the micro-cutter have been demonstrated in polystyrene. However, other plastics/polymers such as polycarbonate

may be used. The mold may be constructed as described above. However, it will be apparent to those skilled in the art that a number of different methods for constructing a mold with the necessary microstructure may be utilized.

Once a substrate with the microprotrusions is constructed, the drug channels 205 may be introduced by a conventional pattern etch. Similarly, a depression for the reservoir 204 may be introduced by an etching operation. The drug may be placed in the reservoir by enclosing a pad on which the drug has been absorbed in the depression. The reservoir may then be sealed with a cover 209 over the reservoir.

While the above embodiments have been described in terms of microprotrusions or microneedles, it will be apparent to those skilled in the art that the protrusions can also be in the shape of blades having a height of approximately 10 to 20 μm and a length of 40 to 200 μm.. Blades have the advantage of being less likely to break during the movement of a micro-cutter relative to the patient's skin. When the device is applied to the patient's skin, it is pressed against the skin and moved parallel to the surface of the skin, thereby introducing a number of small shallow incisions into which the drug from the reservoir will flow. The device is then taped to the patient. Additional movement of the skin relative to the micro-cutters as the patient moves the area on which the device is attached opens additional incisions. However, since these incisions do not extend into a region having blood or nerves, the patient feels no pain.

As noted above, the micro-cutter must be designed so as to disrupt the stratum corneum without interrupting the underlying layers of skin. To accomplish this, the micro-cutter must disrupt, remove or penetrate approximately the top 10 μm of skin and then stop.

While the above-described fabrication techniques utilized silicon substrates to form the microprotrusions directly or through molding of plastics/polymers, metals or the like, it will be apparent to those skilled in the art from the above discussion that microprotrusions may be fabricated as an inexpensive and identical array of microneedles by any one of several technologies known as micromachining, micromechanics, MEMS, etc. These microelectronic-like technologies typically first employ the deposition onto a substrate of

various films on the size scale of the stratum corneum thickness. Examples of typical films include silicon nitride, silicon oxide, polyimide, aluminum, gold, etc. Secondly, a photolithography technique imparts an image of an array of hundreds or thousands of tiny structures to the top film layer. After selective etching, this results in the fabrication of millions of identical microstructures on the size scale of the stratum corneum thickness. Other process steps include wet etching, plasma etching, or reactive ion etching a photosensitive polymer film (resist) on a silicon substrate or wafer as is common in the microelectronics industry. The films may be deposited by chemical vapor deposition techniques prior to the etching operation. The substrate is then bulk and/or surfaced micromachined to achieve the required height tolerance which is preferably 15 ± 2μm.

While the above-described embodiments of the present invention have utilized a micro-cutter that just penetrates the stratum corneum, other embodiments that penetrate deeper may also be used. The epidermis layer under the stratum corneum is approximately 100 μm thick, and like the stratum corneum, has no blood vessels or nerve endings. The epidermis, however, does have live cells that are fed by diffusion from the dermis below. Hence, the micro-cutter can penetrate to a depth of the epidermal/dermal interface without encountering the problems of prior art devices that attempt to disrupt the skin barrier, but damage the dermis layer as well.

As noted above, some chemicals can be forced across the skin by the application of an electric field. This requires that electrodes be placed on the skin and that a potential difference be applied between the reservoir and an underlying layer of skin. Such electrodes can be incorporated into a patch according to the present invention utilizing conventional metal deposition techniques. Exemplary electrodes are shown in Figure 1 at 210. It will be apparent to those skilled in the art that the micro-protrusions can also be utilized as electrodes if the protrusions are constructed from metallic substances or converted to conductors via ion implantation.

It should also be noted that a bed of microprotrusions according to the present invention can be used as an improved electrode. In addition to providing resistance to diffusion, the stratum corneum is a poor electrical conductor. By interrupting the stratum

corneum, the present invention provides an improved conducting path to the underlying layers. If the present invention is to be used as an electrode, the embodiments in which the microprotrusions are conductors or micro-needles are preferred. In the latter case, the reservoir may be filled with a conducting liquid which, in effect, aids the trans-stratum corneum conduction. Alternatively, the reservoir may be omitted.

Various modifications to the present invention will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Accordingly, the present invention is to be limited solely by the scope of the following claims.

WHAT IS CLAIMED:

1. An apparatus[200] for the transdermal delivery of a compound, a plurality of microprotrusions[202] for disrupting a layer of skin, said disruption being accomplished without substantially disrupting underlying dermis layers below said layer of skin, said microprotrusions[202] having a height less than or equal to said thickness of said layer of skin; stop means[206] for preventing said apparatus[200] from penetrating said layer of skin beyond a predetermined distance; and a reservoir[204] having a channel communicating with said layer of skin or one of said underlying dermis layers.

2. The apparatus[200] of Claim 1 wherein said microprotrusions[202] comprise first and second groups of microprotrusions[202] extending from a substrate and wherein said stop means[206] comprises a region of said substrate separating said first and second groups.

3. The apparatus[200] of Claim 1 wherein at least one of said microprotrusions[202] is a blade having a substantially rectangular cross-section in which the length of said rectangle is at least two times the cross-section of said rectangle.

4. The apparatus[200] of Claim 1 wherein said microprotrusions[202] comprise molded polymer or metal microprotrusions[202].

5. The apparatus[200] of Claim 1 wherein said channel comprises a passage through one of said microprotrusions[202].

6. The apparatus[200] of Claim 1 further comprising an electrode located so as to contact said layer of skin or said underlying dermis layer when said microprotrusions[202] are positioned so as to interrupt said layer of skin.

7. A method for the transdermal delivery of a compound comprising the steps of applying an apparatus[200] to a layer of skin, said apparatus[200] comprising a plurality of microprotrusions[202] for disrupting a layer of skin, said disruption being accomplished without substantially disrupting underlying dermis layers below said layer of skin, said

microprotrusions[202] having a height less than or equal to said thickness of said layer of skin; stop means[206] for preventing said apparatus[200] from penetrating said layer of skin beyond a predetermined distance; and a reservoir[204] having a channel communicating with said layer of skin or one of said underlying dermis layers.

8. The method of Claim 7 wherein said microprotrusions[202] comprise first and second groups of microprotrusions[202] extending from a substrate and wherein said stop means[206] comprises a region of said substrate separating said first and second groups.

9. The method of Claim 7 wherein at least one of said microprotrusions[202] is a blade having a substantially rectangular cross-section in which the length of said rectangle is at least two times the cross-section of said rectangle.

10. The method of Claim 7 wherein said microprotrusions[202] comprise molded polymer or metal microprotrusions[202].

11. The method of Claim 7 wherein said channel comprises a passage through one of said microprotrusions[202].

12. The method of Claim 7 wherein said apparatus[200] further comprises an electrode located so as to contact said layer of skin or said underlying dermis layer when said microprotrusions[202] are positioned so as to interrupt said layer of skin and wherein said method further comprises the step of applying a potential difference between said electrode and said underlying layer of skin.

13. An electrode for providing an electrical connection to a body, said electrode comprising: a plurality of microprotrusions[202] for disrupting a layer of skin, said disruption being accomplished without substantially disrupting underlying dermis layers below said layer of skin, said microprotrusions[202] having a height less than or equal to said thickness of said layer of skin; stop means[206] for preventing said apparatus[200] from penetrating said layer of skin beyond a predetermined distance; and an electrical conductor

electrode[210] located so as to contact said layer of skin or said underlying dermis layer when said microprotrusions[202] are positioned so as to interrupt said layer of skin.

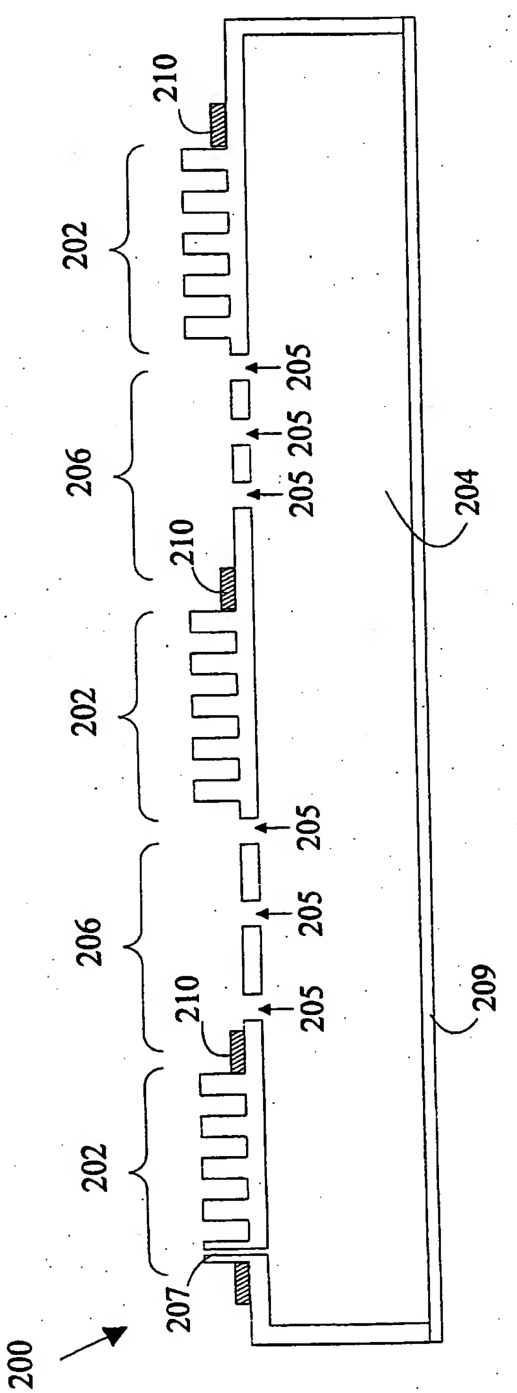

FIGURE 1

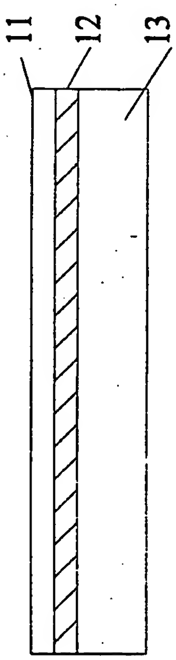

FIGURE 2

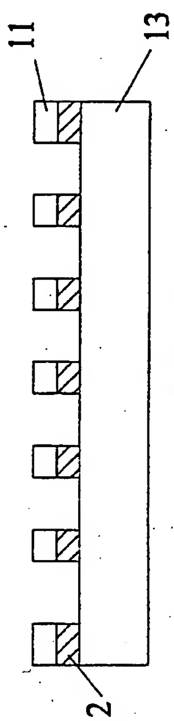

FIGURE 3

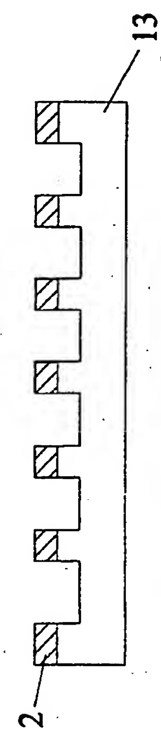

FIGURE 4

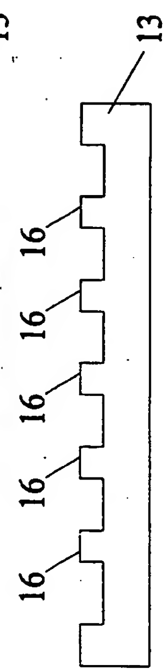

FIGURE 5

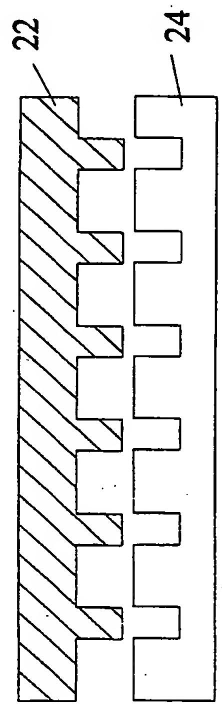

FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61N 1/30
US CL :604/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 449; 604/20, 46

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AS, A, 5,279,544 (GROSS ET AL.) 18 January 1994, see entire reference.	1-13
X	US, A, 3,964,482 (GERTSEL ET AL.) 22 June 1976. see entire document	1-5, 7-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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